REMARKS

Claims 12-14, 16, 18-20, 22, 24, 27, 28 and 30-35 were pending. In this Amendment, claims 18 and 31-35 are amended. Claims 24, 27 and 28 are cancelled, and new claims 36-73 are added. Thus, with this Amendment, claims 12-24, 16, 18-20, 22 and 30-73 are presented for consideration.

The amendment to claim 18 has been made merely to make the language in the preamble consistent with the language in claim 12. It is submitted that no change of claim scope has occurred with the amendment, and the amendment is merely cosmetic. Claims 30-35 have been amended to change the dependencies of these claims, and to broaden the DHA range in accordance with the specification (see page 3, lines 9-11). New independent claims 36 and 43 are presented, which are styled on original claims 12 and 18. New independent claims 50, 56, 62 and 68 are presented, and find support in the claims as originally filed, along with pages 5-6 of the specification. No new matter has been added.

Enablement of New Claims 36, 43, 62 and 68

It is noted that independent claims 36, 43, 62 and 68 are directed to preventing mortality or sudden death of a patient. Claims to similar subject matter were previously presented, and were met with rejections under 35 U.S.C. §112, first paragraph. Essentially, the Examiner took the position that prevention of mortality or sudden death was not enabled by the claims. In order to advance prosecution, applicants address

this issue with respect to the new claims in the event that the Examiner is inclined to apply a similar rejection to the new claims.

The prevention of mortality or sudden death as a clinical endpoint is well-accepted in the art. In fact, several articles published after the effective filing date of the present application support these claims. Applicants refer the Examiner to Attachments 1-4, as discussed in the following paragraphs.

The seminal GISSI-Prevenzione trial, as reported in *Lancet,* 354:447-55 (1999) (Attachment 1), studied over 11,000 patients for two years. The study looked at several efficacy endpoints, including "all-cause death" (i.e., mortality), and cardiovascular death. See page 449, left column, fourth paragraph. As a secondary analysis of cardiovascular deaths, sudden death was measured. See Table 3 on page 450. The study found that, for the combined primary endpoint of death, non-fatal myocardial infarction, and non-fatal stroke, the administration of omega-3 polyunsaturated fatty acids resulted in a significant ($p=0.010$) reduction of events. See page 451, left column, third paragraph. In addition, the study found a significant reduction for sudden death. See page 451, left column, final paragraph. The GISSI-Prevenzione study thus not only indicates that those of ordinary skill in the art understand the terms "mortality" and "sudden death" as used in the present claims, the study also supports the enablement of these claims.

In the article by Albert *et al.*, *N.Engl. J. Med.,* 346(15):1113-18 (2002) (Attachment 2), the authors found that omega-3 fatty acids are strongly associated with

a reduced risk of sudden death. See the "Conclusions" section of the Abstract, page 1113.

Covington, *Am. Family Physician,* 70(1):133-40 (2004) (Attachment 3), noted in the Abstract that "[o]mega-3 fatty acids have been shown to significantly reduce the risk for sudden death caused by cardiac arrhythmias and all-cause mortality in patients with known coronary heart disease."

Finally, in a report prepared for the Agency for Health Care Research and Quality, U.S. Department of Health and Human Services (excerpt at Attachment 4), it was concluded that "consumption of omega-3 fatty acids from fish or from supplements of fish oil reduces all cause mortality and various CVD outcomes." See page vi of the Evidence Report.

Applicants submit that there is overwhelming evidence that claims to preventing mortality or sudden death are fully enabled, and that these claims are allowable.

Obviousness Rejection over Breivik in view of Harrison

In the more recent Office Action of March 9, 2006, the pendent claims were rejected under 35 U.S.C. §103(a) as being unpatentable over Breivik *et al.* (U.S. Patent No. 5,502,077) in view of Harrison's Principals of Internal Medicine, 13th Edition. The Examiner takes the position that Breivik teaches fatty acid compositions containing at least 80% by weight of omega-3 fatty acids, wherein EPA and DHA comprises at least 75% by weight of the total fatty acids, and that the compositions can be used for treating multiple risk factors for cardiovascular diseases. The Examiner admits that Breivik does

not disclose that such risk factors include myocardial infarction or that the patient being treated has already experienced a cardiovascular event. However, the Examiner maintains that because Breivik teach treatment of the risk factors, one of ordinary skill in the art would have appreciated that the incidents of cardiovascular events, such as myocardial infarction, could be reduced. The Examiner points to Harrison as teaching the existence of the claimed patient population (i.e., myocardial infarction survivors), and that the risk factors treated by Breivik include those risk factors known to be associated with myocardial infarction. Thus, the Examiner concludes, one of ordinary skill in the art would have appreciated that Breivik contemplated treating myocardial infarction survivors.

Applicants agree with the Examiner that Breivik teaches the treatment of multiple risk factors for cardiovascular diseases. However, applicants respectfully submit that it would not have been obvious to use omega-3 fatty acids for the prevention of cardiovascular **events** simply because it was known that omega-3 fatty acids were useful for treating cardiovascular **risk factors**. In fact, several major studies have shown that other treatments of cardiovascular risk factors do not necessarily help in the prevention of cardiovascular events.

The drug fenofibrate is known to be used to treat hypercholesterolemia, hypertriglyceridemia and mixed dyslipidemia. See, e.g., the product information for TRICOR® fenofibrate tablets (Attachment 5). It is well known that hypercholesterolemia, hypertriglyceridemia and mixed dyslipidemia are risk factors for cardiovascular diseases. However, in the FIELD study, reported in *Lancet*, 366:1849-

61 (2005) (Attachment 6), it was found that fenofibrate did not significantly reduce coronary events (an endpoint that included coronary heart disease mortality and non-fatal myocardial infarction). In addition, no significant reduction of cardiovascular disease mortality, total mortality or stroke was found. See Table 3 on page 7 of the attached article.

Even more striking evidence can be found in the ALLHAT trial, as reported in *JAMA,* 283:1967-75 (2000) (Attachment 7). ALLHAT compared the effects of doxazosin with chlorthalidone on incidents of cardiovascular disease in patients with hypertension. The primary outcome measured was fatal coronary heart disease or non-fatal myocardial infaction. Secondary outcome measures included all-cause mortality, stroke, and combined cardiovascular disease (which included coronary heart disease death, non-fatal myocardial infarction, stroke, angina, coronary revascularization, congestive heart failure and peripheral arterial disease). See the section entitled "Main Outcome Measures" in the Abstract on page 1967.

Both doxazosin and chlorthalidone are indicated to treat hypertension. See the attached product information sheets for CARDURA® doxazosin tablets, and THALITONE® chlorthalidone tablets (Attachments 8 and 9). It is noted with interest that hypertension is also one of the cardiovascular disease risk factors named by Breivik and Harrison, as indicated by the Examiner in his rejection.

Despite the similar indication for the two drugs studied in the ALLHAT trial, the study reports a statistically significant 25% higher incidence of major cardiovascular disease events in the doxazosin group compared with the chlothalidone group. See

page 1968, left column, second paragraph. In fact, the results were so striking that the doxazosin arm of the trial was discontinued. See page 1972, left column, second paragraph.

Applicants respectfully submit that these papers evidence that it would not have been obvious to use omega-3 fatty acids in the prevention of adverse cardiovascular events simply because it was known that omega-3 fatty acids are useful to treat cardiovascular risk factors. Applicants request that the rejection be withdrawn.

CONCLUSION

Applicants submit that the application is in condition for allowance and request favorable action thereon.

Enclosed is a Petition of Time (4 months). However, the Commissioner is hereby authorized to charge any required fees to Deposit Account No. 08-0750. Further, if there is any other fee deficiency or overpayment of any fees in connection with this patent application, the Commissioner is hereby authorized to charge such deficiency or credit such overpayment to Deposit Account No. 08-0750.

Respectfully submitted,

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CERTIFICATE OF MAILING UNDER 37 C.F.R. §1.8

I certify that this correspondence is being deposited with the U.S. Postal Service on **December 8, 2006** with sufficient postage as first class mail (including Express Mail per MPEP §512), and addressed to **Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450**.

James E. Davis